

WHAT IS CLAIMED IS:

1 1. A leptin receptor (OB-R) polypeptide.

1 2. The leptin receptor of claim 1 characterized by

2 a) specific binding to leptin under physiological conditions;

3 b) expression at high levels in cells of the hypothalamus, and

4 expression at lower levels in adipose tissue, testes, heart, and brain; and

5 c) having sequence similarity to gp130 cytokine receptors.

1 3. The leptin receptor of claim 1 which is encoded by a nucleic acid which is

2 identifiable with a polymerase chain reaction (PCR) probe selected from group

3 consisting of a probe for clone 7 (forward primer SEQ ID NO:42 and reverse

4 primer SEQ ID NO:43), a probe for clone 11 (forward primer SEQ ID NO:44 and

5 reverse primer SEQ ID NO:45), and both clone 7 and clone 11.

1 4. The leptin receptor of claim 3, which is encoded by a nucleic acid which is

2 identifiable with a PCR probe selected from the group consisting of a probe for

3 clone 42 (forward primer SEQ ID NO:26 and reverse primer SEQ ID NO:46); a

4 probe for clone 46 (forward primer SEQ ID NO:47 and reverse primer SEQ ID

5 NO:48); a probe for clone 58 (forward primer SEQ ID NO:47 and reverse primer

6 SEQ ID NO:50); a probe for clone S14 (forward primer SEQ ID NO:51 and

7 reverse primer SEQ ID NO:52); and a probe for clone S3 (forward primer SEQ

8 ID NO:53 and reverse primer SEQ ID NO:54).

1 5. The leptin receptor of claim 1 which is selected from the group consisting

2 of OB-Ra, OB-Rb, OB-Rc, OB-Rd, and OB-Re, or allelic variants thereof.

1 6. The leptin receptor of claim 1 which is selected from the group consisting

2 of:

3 a) N-terminal corresponding to OB-Ra through Lys⁸⁸⁹ and C-terminal
4 corresponding to a C-terminal selected from the group consisting of OB-
5 Rb, OB-Rc, and OB-Rd after Lys⁸⁸⁹;
6 b) N-terminal corresponding to OB-Rb or OB-Rc through Lys⁸⁸⁹, and
7 C-terminal corresponding to OB-Ra or OB-Rd after Lys⁸⁸⁹;
8 c) N-terminal corresponding to OB-Rd through Lys⁸⁸⁹, and C-terminal
9 corresponding to OB-Ra, OB-Rb, or OB-Rc;
10 d) N-terminal corresponding to OB-R from Pro⁶⁶⁴ to Lys⁸⁸⁹, and C-
11 terminal corresponding to OB-Ra, OB-Rb, OB-Rc, and OB-Rd;
12 e) N-terminal corresponding to OB-R from Met⁷³³ to Lys⁸⁸⁹, and C-
13 terminal corresponding to OB-Ra, OB-Rb, OB-Rc, and OB-Rd;
14 f) N-terminal selected from the group consisting of OB-Ra, OB-Rb,
15 OB-Rd, and OB-R from Pro⁶⁶⁴, to His⁷⁹⁶, and OB-Re from His⁷⁹⁶;
16 g) N-terminal corresponding to OB-R from Met⁷³³ to His⁷⁹⁶, and OB-Re
17 from His⁷⁹⁶, or allelic variants thereof.

1 7. The leptin receptor of claim 1 wherein
2 a) the N-terminal sequence is selected from the group consisting of
3 i) amino acid residues 1-889;
4 ii) amino acid residues 23-889;
5 iii) amino acid residues 28-889;
6 iv) amino acid residues 133-889;
7 v) amino acid residues 733-889;
8 vi) amino acid residues 1-796;
9 vii) amino acid residues 23-796;
10 viii) amino acid residues 28-796;
11 ix) amino acid residues 133-796; and
12 x) amino acid residues 733-796; and
13 b) the C-terminal sequence is selected from the group consisting of
14 i) SEQ ID NO:11;
15 ii) SEQ ID NO:12;

19 wherein the numbering is based on the amino acid sequence of the full length
20 transcribed murine leptin receptor, including the signal peptide, or allelic variants
21 thereof.

1 8. The leptin receptor of claim 1 which is a soluble receptor.

1 9. The leptin receptor of claim 8 which is selected from the group consisting
2 of

3 a) OB-Re;

4 b) an N-terminal sequence which is selected from the group consisting of

5 OB-Ra, OB-Rb, OB-Rd, and OB-R from Pro⁶⁶⁴, through His⁷⁹⁹, and a C-

6 terminal sequence which is OB-Re from His⁷⁹⁶;

7 c) an N-terminal sequence which is selected from the group consisting

8 of

9 i) amino acid residues 1-796;

0 ii) amino acid residues 23-796;

1 iii) amino acid residues 28-796;

2 iv) amino acid residues 133-796; and

3 v) amino acid residues 733-796; and

4 a C-terminal sequence which is SEQ ID NO:15;

15 wherein the numbering is based on the amino acid sequence of the full length
16 transcribed murine leptin receptor, including the signal peptide, or allelic variants
17 thereof.

1 10. The leptin receptor of claim 1 which comprises a transmembrane domain,
2 and is an integral membrane protein.

1 11. The leptin receptor of claim 10 which further comprises a JAK binding
2 motif selected from "Box 1," "Box 2," and "Box 1" and "Box 2", which motif is
3 downstream of the transmembrane domain.

1 12. The leptin receptor of claim 1 which is a human leptin receptor.

1 13. The leptin receptor of claim 1 which is a murine leptin receptor.

1 14. The leptin receptor of claim 12 comprising an amino acid substitution
2 selected from the group consisting of: Phe for Ser³⁶; Asp for Tyr⁴⁴; Ser for Leu⁴⁹;
3 Pro for Ser⁵⁴; Leu for Ser⁶⁰; Ala for His⁶³; Ala for Thr⁶⁶; Ala for Pro⁷⁰; Ile for
4 Thr⁷⁷; Tyr for His⁷⁸; Pro for Ser⁸⁰; Gly for Arg⁹²; Gly for Asp⁹⁶; Thr for Ala¹⁰³ or
5 Ile¹⁰⁶; Ser for Leu¹¹⁸; Gly for Asp¹²⁴; Thr for Lys¹³⁸; Pro for Ser¹⁴⁶; Asp for Val¹⁶⁴;
6 Leu for Gln¹⁷⁷; Asp for Gly¹⁷⁹; Gly for Glu¹⁹²; deletion for Cys¹⁹³; His for Leu¹⁹⁷;
7 Ser for Ile²²¹; Leu for Asn²³³; Leu for Ser²⁷³; deletion for Thr²⁷⁸; Ala for Asp²⁸⁵;
8 Glu for Lys²⁸⁶; Ser for Gly³¹⁰; Arg for Met³⁷⁰; Ile for Ser³⁷⁹; Ser for Phe³⁹⁴; Ala for
9 Glu⁴¹⁷; Gly for Glu⁴⁵⁹; Ser for Ile⁴⁷⁶; Thr for Ile⁴⁸²; Thr for Ile⁵⁵¹; His for Tyr⁵⁸⁶;
10 Lys for Ile⁶⁴⁸; Ala for Ser⁶⁸⁶; His for Cys⁶⁸⁷; Thr for Ile⁷⁵⁹; Ile for Asn⁷⁷⁶; Asp for
11 Gly⁷⁸¹; Gly for Glu⁷⁸²; Gly for Ser⁸²⁷; Ala for Asp⁸³²; Arg for Pro⁸⁹²; Thr for
12 Glu⁸⁹³; Asp for Thr⁸⁹⁴; or Leu for Glu⁸⁹⁶, wherein the numbering of the amino
13 acids corresponds to the numbering adopted for the human leptin receptor,
14 including the signal sequence.

1 15. An antigenic fragment of the leptin receptor of claim 1.

1 16. The antigenic fragment of claim 15 which is selected from the group
2 consisting of SEQ ID NO:32, SEQ ID NO:33, and SEQ ID NO:34.

1 17. A derivative of the leptin receptor of claim 8 or 9 attached to a chemical
2 moiety.

1 18. The derivative of claim 15 wherein the chemical moiety is a water-soluble
2 polymer.

1 19. The derivative of claim 16 wherein the water soluble polymer is
2 polyethylene glycol.

1 20. An isolated nucleic acid encoding a leptin receptor of claim 1.

1 21. An isolated nucleic acid encoding a leptin receptor of claim 5, 6, or 7.

1 22. An isolated nucleic acid encoding a leptin receptor of claim 8 or 9.

1 23. An isolated nucleic acid encoding a leptin receptor of claim 10 or 11.

1 24. An isolated DNA molecule encoding on expression a leptin receptor
2 polypeptide selected from the group consisting of:
3 a) a polypeptide coding sequence of a DNA molecule of SEQ ID
4 NO:1, 3, 5, 7, or 9;
5 b) a DNA molecule complementary to the DNA molecule defined in
6 (a);
7 c) a DNA molecule which hybridizes to the DNA molecule of (a) or
8 (b), or a hybridizable fragment thereof;
9 d) a DNA molecule which is identifiable with a polymerase chain
10 reaction (PCR) probe selected from group consisting of a probe for clone 7
11 (forward primer SEQ ID NO:42 and reverse primer SEQ ID NO:43), a
12 probe for clone 11 (forward primer SEQ ID NO:44 and reverse primer
13 SEQ ID NO:45), and both clone 7 and clone 11; and
14 e) a DNA molecule that codes on expression for the polypeptide
15 encoded by any of the foregoing DNA molecules.

1 25. The DNA molecule of claim 24 which is human.

1 26. The DNA molecule of claim 24 which is murine.

1 27. The DNA molecule of claim 24 which codes on expression for a
2 polypeptide selected from the group consisting of:

3 a) a leptin receptor selected from the group consisting of OB-Ra, OB-
4 Rb, OB-Rc, OB-Rd, and OB-Re, or allelic variants thereof;

5 b) a leptin receptor selected from the group consisting of:

6 i) N-terminal corresponding to OB-Ra through Lys⁸⁸⁹ and C-
7 terminal corresponding to a C-terminal selected from the group
8 consisting of OB-Rb, OB-Rc, and OB-Rd after Lys⁸⁸⁹;

9 ii) N-terminal corresponding to OB-Rb or OB-Rc through
10 Lys⁸⁸⁹, and C-terminal corresponding to OB-Ra or OB-Rd after
11 Lys⁸⁸⁹;

12 iii) N-terminal corresponding to OB-Rd through Lys⁸⁸⁹, and C-
13 terminal corresponding to OB-Ra, OB-Rb, or OB-Rc;

14 iv) N-terminal corresponding to OB-R from Pro⁶⁶⁴ to Lys⁸⁸⁹, and
15 C-terminal corresponding to OB-Ra, OB-Rb, OB-Rc, and OB-Rd;

16 v) N-terminal corresponding to OB-R from Met⁷³³ to Lys⁸⁸⁹, and
17 C-terminal corresponding to OB-Ra, OB-Rb, OB-Rc, and OB-Rd;

18 vi) N-terminal selected from the group consisting of OB-Ra,
19 OB-Rb, OB-Rd, and OB-R from Pro⁶⁶⁴, through His⁷⁹⁶, and OB-Re
20 from His⁷⁹⁶, and

21 vii) N-terminal corresponding to OB-R from Met⁷³³ to His⁷⁹⁶, and
22 OB-Re from His⁷⁹⁶,

23 or allelic variants thereof;

24 c) a leptin receptor wherein

25 i) the N-terminal sequence is selected from the group consisting
26 of

27 (1) amino acid residues 1-889;

28 (2) amino acid residues 23-889;

29 (3) amino acid residues 28-889;

30 (4) amino acid residues 133-889;
31 (5) amino acid residues 733-889;
32 (6) amino acid residues 1-796;
33 (7) amino acid residues 23-796;
34 (8) amino acid residues 28-796;
35 (9) amino acid residues 133-796; and
36 (10) amino acid residues 733-796; and
37 ii) the C-terminal sequence is selected from the group consisting
38 of
39 (1) SEQ ID NO:11;
40 (2) SEQ ID NO:12;
41 (3) SEQ ID NO:13;
42 (4) SEQ ID NO:14; and
43 (5) SEQ ID NO:15;

44 wherein the numbering is based on the amino acid sequence of the full
45 length transcribed murine leptin receptor, including the signal peptide, or
46 allelic variants thereof.

1 28. A nucleic acid molecule having a nucleotide sequence corresponding or
2 complementary to the DNA sequence set forth in SEQ ID NO:1, 3, 5, 7 or 9.

1 29. An oligonucleotide hybridizable under stringent conditions to the nucleic
2 acid molecule of claim 24.

1 30. An oligonucleotide hybridizable under stringent conditions to the nucleic
2 acid molecule of claim 27.

1 31. An oligonucleotide hybridizable under stringent conditions to the nucleic
2 acid molecule of claim 28.

1 32. The oligonucleotide of claim 29, 30, or 31 selected from the group
2 consisting of SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23,
3 SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID
4 NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:35, SEQ
5 ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40,
6 SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID
7 NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ
8 ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, and SEQ ID
9 NO:54.

1 33. The oligonucleotide of claim 32 which is labeled.

1 34. The nucleic acid of claim 20, 21, 22, or 23 which is DNA.

1 35. A vector comprising the DNA of claim 34.

1 36. A vector comprising the DNA of claim 24, 27, or 28.

1 37. An expression vector which comprises the DNA of claim 34, operatively
2 associated with an expression control sequence.

1 38. An expression vector which comprises the DNA of claim 24, 27, or 28,
2 operatively associated with an expression control sequence.

1 39. An unicellular host transformed or transfected with a DNA molecule of
2 claim 34.

1 40. An unicellular host transformed or transfected with a DNA molecule of
2 claim 24, 27, or 28.

1 41. An unicellular host transformed or transfected with an expression vector of
2 claim 37.

1 42. An unicellular host transformed or transfected with an expression vector of
2 claim 38.

1 43. The unicellular host of claim 41 selected from the group consisting of
2 bacteria, yeast, mammalian cells, plant cells, and insect cells, in tissue culture.

1 44. The unicellular host of claim 42 selected from the group consisting of
2 bacteria, yeast, mammalian cells, plant cells, and insect cells, in tissue culture.

1 45. The unicellular host of claim 43, wherein the unicellular host is selected
2 from the group consisting of *E. coli*, *Pseudomonas*, *Bacillus*, *Streptomyces*,
3 *Saccharomyces*, *Pichia*, *Candida*, *Hansenula*, *Torulopsis*, CHO, R1.1, B-W, LM,
4 COS 1, COS 7, BSC1, BSC40, BMT10, and Sf9 cells.

1 46. The unicellular host of claim 44, wherein the unicellular host is selected
2 from the group consisting of *E. coli*, *Pseudomonas*, *Bacillus*, *Streptomyces*,
3 *Saccharomyces*, *Pichia*, *Candida*, *Hansenula*, *Torulopsis*, CHO, R1.1, B-W, LM,
4 COS 1, COS 7, BSC1, BSC40, BMT10, and Sf9 cells.

1 47. A method for preparing a leptin receptor polypeptide comprising:
2 a) culturing a cell according to any claim 43 under conditions that
3 provide for expression of the leptin receptor polypeptide; and
4 b) recovering the expressed polypeptide.

1 48. A method for preparing a leptin receptor polypeptide comprising:
2 a) culturing a cell according to any claim 44 under conditions that
3 provide for expression of the leptin receptor polypeptide; and
4 b) recovering the expressed polypeptide.

1 49. The oligonucleotide of claim 29, 30, or 31 which is an antisense nucleic
2 acid that hybridizes with an mRNA encoding leptin receptor.

1 50. A ribozyme which cleaves an mRNA encoding a leptin receptor.

1 51. A transgenic vector comprising a DNA molecule of claim 34.

1 52. A transgenic vector comprising a DNA molecule of claim 24, 27, or 28.

1 53. An antibody specific for a leptin receptor of claim 1.

1 54. An antibody according to claim 53 which is a monoclonal or polyclonal
2 antibody.

1 55. An antibody according to claim 53 labeled with a detectable label.

1 56. An immortal cell line that produces a monoclonal antibody according to
2 claim 54.

1 57. A method for preparing an antibody specific for a leptin receptor,
2 comprising:

3 a) immunizing a host animal with the leptin receptor of claim 1
4 admixed with an adjuvant; and
5 b) obtaining antibody from the immunized host animal.

1 58. A method for preparing an antibody specific for a leptin receptor,
2 comprising:
3 a) conjugating a peptide having a sequence selected from the group
4 consisting of SEQ ID NO:32, SEQ ID NO:33, and SEQ ID NO:34 to a
5 carrier protein;

- 6 b) immunizing a host animal with the peptide-carrier protein conjugate
- 7 of step (a) admixed with an adjuvant; and
- 8 c) obtaining antibody from the immunized host animal.

1 59. A method for measuring the presence of a leptin receptor in a sample,
2 comprising:

- 3 a) contacting a sample suspected of containing a leptin receptor with an
- 4 antibody that specifically binds to the leptin receptor under conditions
- 5 which allow for the formation of reaction complexes comprising the
- 6 antibody and the leptin receptor; and
- 7 b) detecting the formation of reaction complexes comprising the
- 8 antibody and leptin receptor in the sample,

9 wherein detection of the formation of reaction complexes indicates the presence of
10 leptin receptor in the sample.

1 60. The method according to claim 59 wherein the antibody is bound to a solid
2 phase support.

1 61. An *in vitro* method for evaluating the level of leptin receptor in a biological
2 sample comprising:

- 3 a) detecting the formation of reaction complexes in a biological sample
- 4 according to the method of claim 59 or 60; and
- 5 b) evaluating the amount of reaction complexes formed, which amount
- 6 of reaction complexes corresponds to the level of leptin receptor in the
- 7 biological sample.

1 62. An *in vitro* method for detecting or diagnosing the presence of a disease
2 associated with elevated or decreased levels of leptin receptor in a subject
3 comprising:

4 a) evaluating the level of leptin receptor in a biological sample from a
5 subject according to claim 61; and
6 b) comparing the level detected in step (a) to a level of leptin receptor
7 present in normal subjects or in the subject at an earlier time,
8 wherein an increase in the level of leptin receptor as compared to normal levels
9 indicates a disease associated with elevated levels of leptin receptor, and decreased
10 level of leptin receptor as compared to normal levels indicates a disease associated
11 with decreased levels of leptin receptor.

1 63. A pharmaceutical composition comprising a soluble leptin receptor
2 according to any of claims 8 or 9, and a pharmaceutically acceptable carrier.

1 64. A method for treating obesity in a subject comprising administering a
2 therapeutically effective amount of the pharmaceutical composition of claim 63.

1 65. The method according to claim 64, further comprising administering a
2 treatment for diabetes, high blood pressure, and high cholesterol.

1 66. A body appearance improving cosmetic composition for reducing the body
2 weight of an individual comprising a soluble leptin receptor of claim 8 or 9, and
3 an acceptable carrier.

Add a 